PERGAMON

Food and Chemical Toxicology 38 (2000) 79–98

Food and Chemical Toxicology

www.elsevier.com/locate/foodchemtox

Review

Review of the Toxicologic Properties of Medium-chain Triglycerides

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(*Accepted 16 June 1999*)

Summary—**Medium chain triglycerides (MCTs) are a family of triglycerides, containing predominantly, caprylic (C_8) and capric (C_{10}) fatty acids with lesser amounts of caproic (C_6) and lauric (C_{12}) fatty acids. MCTs are widely used for parenteral nutrition in individuals requiring supplemental nutrition and are being more widely used in foods, drugs and cosmetics. MCTs are essentially non-toxic in acute toxicity tests conducted in several species of animals. In ocular and dermal irritation testing MCTs exhibit virtually no potential as ocular or dermal irritants, even with prolonged eye or skin exposure. MCTs exhibit no capacity for induction of hypersensitivity. Ninety-day toxicity tests did not result in notable toxicity, whether the product was administered in the diet up to 9375 mg/kg body weight/day or by intramuscular (im) injection (up to 0.5 ml/kg/day, rabbits). There was no evidence that intravenous (iv) or dietary administration of MCTs adversely affected the reproductive performance of rats or resulted in maternal toxicity, foetal toxicity or teratogenic effects at doses up to 4.28 g/kg body weight/day (iv) or 12,500 mg/kg body weight/day (dietary). There was no evidence that dietary administration of MCTs adversely affected the reproductive performance of pigs or resulted in maternal toxicity, foetal toxicity or teratogenic effects at doses up to 4000 mg/kg body weight/day in the diet. In rabbits, following iv administration, the maternal and foetal no-observed-adverse-effect levels (NOAELs) were between 1.0 and 4.28 g/kg body weight/ day. A 2-year study in rats, conducted with a closely related compound (tricaprylin, a triglyceride with C_8 fatty acids), provided no evidence of a carcinogenic effect when the material was administered by oral gavage at levels up to 10 ml/kg (9.54 g/kg) per day. Although tricaprylin was found to be positive in one of five strains of *Salmonella typhimurium* in the presence of metabolic activation in an Ames mutagenicity assay, the results of the carcinogenicity test with tricaprylin and mutagenicity tests with caprylic acid indicate that MCTs do not have the potential to be carcinogenic or mutagenic. The safety of human dietary consumption of MCTs, up to levels of 1 g/kg, has been confirmed in several clinical trials.** *© 2000 Elsevier Science Ltd. All rights reserved*

Keywords: triglycerides; MCT; toxicology.

Abbreviations: LAK = lymphokine-activated killer; LCT = long-chain triglycerides; MCFA = medium-chain fatty acids; MCT = medium-chain triglycerides; NK = natural killer; NOAEL = no-observed-adverse-effect levels; PII = primary irritation index; TPN = total parenteral nutrition

Introduction

Medium-chain triglycerides (MCTs) are a family of triglycerides, composed mainly of caprylic (C_8; 50–80%) and capric fatty acids (C_{10}; 20–50%) with a minor contribution of caproic (C_6; 1–2%) and lauric (C_{12}; 1–2%) fatty acids (Bach and Babayan, 1982). MCTs are produced conventionally by splitting and distilling the fatty acids from coconut or palm kernel oils. The fatty acids are then mixed in a desired ratio and esterified with glycerin to form a triglyceride. MCTs were first introduced into the clinical arena approximately 50 years ago. Their original use was as a substitute for long-chain triglycerides (LCT) in the treatment of disorders of lipid absorption. Since that time, MCTs have been utilized in an increasing number of food and nutrition applications because they have been found to offer a number of advantages over LCTs. MCTs are also used primarily as emulsifiers, in various human and veterinary pharmaceutical preparations and in cosmetics; however, they are being utilized in an increasing number of food applications as well. In June 1994, a GRAS affirmation petition for use of MCTs in food products was accepted by the US

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0278-6915/00/$ - see front matter © 2000 Elsevier Science Ltd. All rights reserved. Printed in Great Britain
PII S0278-6915(99)00106-4

Food and Drug Administration. Captrin is the proposed name for the randomized triglycerides of primarily C_8 and C_{10} fatty acids that are the subject of that petition.

There is a large number of animal and human studies that examine various metabolic and general health aspects of MCT consumption. Although most of those studies do not directly examine the toxicological safety of MCTs and are not reviewed here, they do document the widespread safe historical consumption of MCTs.

It is the purpose of this review to consolidate and summarize safety data from a variety of studies with MCTs in animals and in humans. We acknowledge that reviews have been presented earlier (Bach and Babayan, 1982; CTFA, 1980), however there are some critical studies conducted since those reviews were prepared. Emphasis is placed on newer data, when that became available. The toxicological profile for MCTs was derived from studies which utilized purified caprie or caprylic fatty acids in addition to studies involving various mixed ester MCTs.

Chemical and physical properties

Neobee® M-5, Captex® 300 and Miglyol® 812, representative MCTs, are described as clear, pale yellow to water white, odourless, oily liquids with characteristics listed in Table 1.

Methods for testing MCTs involve determining the principal components (fatty acid content by gas liquid chromatographic analysis) and secondary components (water by Karl Fischer); and chemical and physical characteristics (unsaponifiable fatty acids, acid number, saponification value, iodine number, iodine colour number, hydroxyl value and peroxide number all by standard colorimetric methods) (Paghoeca, 1998b). Three samples of Miglyol 812 contained no detectable levels (detection limits 5 ppb) of aflatoxin B_1 (Fritsch, 1977).

Absorption, distribution and metabolism

Absorption and distribution

MCTs are partially hydrolysed by lingual lipase in the stomach and then rapidly and efficiently by pancreatic lipase within the intestinal lumen, thereby allowing for the direct absorption of medium-chain fatty acids (MCFAs) via the portal vein to the liver rather than through the thoracic duct lymph system which is the conventional route for the absorption of triglycerides containing long-chain fatty acids. A minor fraction of MCFAs bypass the liver and are distributed to peripheral tissues via the general circulation (Babayan, 1988; Bach and Babayan, 1982; Greenberger and Skillman, 1969). The MCFAs are catabolized predominantly in the liver to C_2 fragments. The C_2 fragments are further converted to CO_2 or used to synthesize longer-chain fatty acids. Very little of the MCT, if any, is stored in adipose tissues (CTFA, 1980; Greenberger and Skillman, 1969). There are no published data available concerning absorption and metabolism of MCT following topical application. It has been reported, however, that if MCTs are subjected to high-pressure submicronization, they can provide an effective vehicle for drugs to be absorbed through the skin (Schwartz *et al.*, 1995). Any portion of an applied dose that would be absorbed would probably be metabolized by the liver. The available information on the absorption and metabolism of MCTs suggests that MCTs injected into muscle could be absorbed into the blood stream and transported to the liver for metabolism and breakdown.

Table 1. Properties of representative medium chain triglycerides

Composition	Neobee M-5[a]	Captex 300[b]	Miglyol 812[c]
Caproic acid $C_5H_{11}COOH$ 6.0	maximum 3%	3	maximum 5%
Caprylic acid $C_7H_{15}COOH$ 8.0	65–75%	68	50–65%
Capric acid $C_9H_{19}COOH$ 10.0	23–33%	28	30–45%
Lauric acid $C_{11}H_{23}COOH$ 12.0	maximum 2.5%	1	maximum 5%
Chemical and physical properties			
Acid value	maximum 0.2	0.1	maximum 0.1
Saponification value	340	335–350	325–345
Iodine value	Maximum 1.0	0.5	maximum 1.0
Unsaponifiable matter	n.s.	n.s.	maximum 0.3%
Iodine colour value	n.s.	n.s.	maximum 2
Cloud point	< −5 C	< −2 C	−10 C
Moisture	maximum 0.2%	maximum 0.1%	maximum 0.15%
Density at 20 C	0.94–0.95	n.s.	0.94–0.96
Refraction at 20 C	1.447	1.4481	1.448–1.450
Viscosity at 20 C	25–30 mPas	24–30 mPas	28–32 mPas
Solubility in water	insoluble	insoluble	insoluble
Solubility in organic solvents	readily soluble	readily soluble	readily soluble

n.s. = not specified.
[a] Neobee is a registered trademark of Stepan Company.
[b] Captex is a registered trademark of Abitec Corp.
[c] Miglyol is a registered trademark of Condea, Inc.
Source: (Babayan, 1987; CTFA, 1980; Paghoeca, 1998a; Palmer, 1991).

In contrast, LCTs are converted to long-chain fatty acids (LCFAs) (e.g. C_{16}-C_{18}, which are the primary fatty acids in dairy fat, meat fat and vegetable oil fat) and monoacylglycerol in the intestinal lumen. These are, in turn, incorporated into chylomicrons and absorbed via the lymphatic system. Chylomicrons eventually reach the general circulation and are distributed to extrahepatic tissues where they are metabolised to LCFAs by the action of lipoprotein lipase; the resulting 'free' LCFAs reach the liver via the systemic circulation. In the presence of pancreatic lipase or bile salt deficiency, MCTs can still be absorbed whereas LCTs cannot (Bach and Babayan, 1982). They also have a carnitine-independent entry into mitochondria and undergo rapid β-oxidation to furnish energy for the cell (Babayan, 1987; Greenberger and Skillman, 1969). Consequently, the MCTs are being used extensively in human nutrition as a source of energy for individuals with malabsorption syndromes, for use in infant formulas and for total parenteral nutrition.

Metabolism

The hepatic mitochondrial metabolism of MCFAs such as caprylic and capric acid ultimately results in an excess of acetyl-CoA which in turn results in the production of acetate, CO_2 and ketone bodies, with a minor portion serving to lengthen endogenous fatty acids (Bach and Babayan, 1982). However, some investigators have suggested that MCT diets, when fed in excess of caloric needs, might lead to increased *de novo* fatty acid synthesis and enhanced fatty acid elongation activity in the liver (Hill *et al.*, 1990). The majority of the MCFAs are catabolized within the liver with only a minor portion reaching the general circulation bound to albumin.

It has been established that consumption of MCTs can lead to ketone production, but it is generally accepted that there is no risk of ketoacidosis or ketonaemia with MCTs at levels associated with normal consumption levels. Patients with liver cirrhosis do not utilize MCTs or their resulting fatty acid components as efficiently as healthy individuals, resulting in higher levels of circulating caprylic acid. Although very high circulating levels of caprylic acid can cause central nervous system toxicity (coma), these concentrations are not achieved from consuming MCTs, even at levels higher than would normally be found in food products (e.g. about 10–15% in baked goods) (Bach and Babayan, 1982; Bach *et al.*, 1977; Freund and Weinster, 1966).

MCT-based diets have been shown to cause minor alterations in serum lipid profiles, and have occasionally yielded slower rates of weight gain relative to LCT-based diets. Experimental studies in both animals and man have shown that MCT-based diets do not cause significant toxicity, even when the diets have consisted of upwards of 5% MCTs. Studies in adults have indicated that MCT-based diets yield lower cholesterol levels relative to LCT-based diets; in addition, MCT-based diets produced smaller increases in plasma triglycerides. In low birth weight infants, MCTs have been shown to improve fat absorption in the absence of a significant change in body weight. The results of some of these nutritional studies can be attributed to the fact that: (1) MCTs are calorically less dense than LCTs; (2) the energy retention of MCT-based diets has been shown to be less than that of LCT-based diets; and (3) the thermic response to food (TRF) is greater after an MCT-based meal. None of the foregoing effects is considered clinically adverse. Animal and clinical studies have also shown that MCTs do not have a significant effect on the absorption of vitamins A, D or E.

The potential effects of dietary MCTs on the absorption of minerals from the intestine have been examined in several studies.

A randomized study with low-birth-weight infants investigated the effect of MCT on 25-hydroxy vitamin D serum levels as well as the absorption and retention of calcium and phosphorus. In this study, 20 infants received a high calcium- and vitamin D-containing formula that contained 50% of its fat as either MCT or LCT. All infants began oral feedings before 7 days of age by intermittent gavage, and feedings were advanced to a goal of 150 ml/kg/day. Blood samples were obtained within the initial 24 hr of the feedings, within 24 hr of reaching a feeding level of 140 ml/kg/day, and at two additional time points after reaching the target consumption of 150 ml/kg/day. Serum data for 25-hydroxy vitamin D showed no significant differences between the two groups at any of the sampling periods. Approximately 1 wk after attaining full feeding volumes, a 96-hr metabolic balance study was initiated. Calcium and phosphorus levels were determined in stools, urine and blood and these data were used to compare intake, absorption and retention for the MCT and LCT groups. There were no significant differences in the percent absorption or retention of calcium or phosphorus between the two groups (Huston *et al.*, 1983).

The effect of MCT- and LCT-containing formulas on calcium, phosphorus and magnesium balances and plasma levels of 1,25-dihydroxy vitamin D was investigated with 28 very-low-birth weight infants. Infants were randomized before the introduction of oral feeding to receive either a pre-term formula in which 40% of the fat consisted of LCTs (MCT group; n = 15) or a formula with a similar total fat content but contained only 6% MCTs (LCT group; n = 13). Feedings were gradually introduced on day 7 by continuous nasogastric lavage until an intake of 150 ml/kg/day was reached at days 16–19. Two 72-hr balance studies were car-

ried out within approximately 2 wk of achieving the target intake level, which involved an analysis of blood, stools and urine levels for Ca, P, Mg and 1,25-dihydroxy vitamin D. The absorption and retention of Ca and Mg were approximately 10–20% higher in the MCT group. The retention of phosphorus was approximately 15% lower in the LCT group, possibly due to a compensating increased urinary excretion of phosphate caused by the lower Ca absorption. There was no significant difference in the plasma levels of 1,25-dihydroxy vitamin D between the two groups (Sulkers *et al.*, 1992).

Keyayoglou *et al.* (1973) concluded that MCT-based diets do not alter Ca absorption. This study involved 10 adult patients who were administered 10 μCi ^{47}CaCl$_2$ in water after an overnight fast. Total body retention of ^{47}Ca was determined from total body counts at 3 hr and 7 days post-treatment, before and after a 4-wk treatment with a low fat diet supplemented with 60 ml day of an oily preparation of MCT (caprylic 23.2%, capric 59.4% and lauric 17.4%). The mean 7-day retention of ^{47}Ca was not different before and after the MCT treatment.

The findings of a study carried out by Tantibhedhyangkul and Hashim (1978) contrasted with the findings of Huston *et al.* (1983). Their study involved 34 low-birth-weight infants who were divided into three groups that received formulas similar in nutrient value but differed with respect to the fat sources. Group one (control) received corn oil, oleo and coconut oil (39:41.20); group two (40% MCT) received MCT, corn oil and coconut oil (40:40:20) and group three (80% MCT) received MCT and corn oil (80:20). Formula feeding began within the first week of life and was continued throughout the hospital stay, which ranged from 28 to 60 days. Stool and urine samples were collected during the second week of life and during the final week of hospitalization, and were analysed for calcium and magnesium levels. The mean calcium absorption, expressed as a percent of dietary calcium, was significantly increased (approx. 50–100%) in both of the MCT groups relative to control; magnesium absorption was significantly increased (approx. 50%) in the 80% MCT group relative to control. There was no significant difference in urinary calcium excretion, expressed per unit of urinary creatinine, among the three groups. Urinary magnesium excretion was comparable between the control and MCT groups.

Clinical trials have indicated that normal dietary levels of MCTs have no adverse effect on the absorption and retention of calcium, magnesium or phosphorus. In several studies, enhanced absorption and retention of these minerals occurred, but this is not considered to be clinically adverse. Most of these studies have been conducted on infants wherein MCTs supplied only a portion (50%) of the fat content of the diet. However, considering that infants have the largest consumption of fat on a body weight basis, the dietary levels of MCT in other population groups would also not be expected to have adverse effects on vitamin and mineral levels. Therefore, the reported increase in absorption of calcium, magnesium and phosphorus following MCT consumption remains inconclusive, but is not considered to be an adverse effect.

Toxicology evaluation of medium-chain triglycerides

MCTs have been evaluated in acute and subchronic toxicity tests using oral, dermal, intraperitoneal, inhalation or intramuscular routes of administration. These materials are used extensively in products that are administered to humans by the oral, topical and intravenous routes. This document summarizes the available information pertaining to the mammalian toxicity of MCTs derived primarily from studies in which Neobee M-5 or Miglyol 812 were the test materials. Additionally, studies are included in which products identified only as medium-chain triglycerides (MCTs) or caprylic/capric triglycerides, which share the general specifications for Neobee M-5 and Miglyol 812, were the test materials.

Oral toxicity

The acute oral toxicity of MCTs (caprylic/capric triglyceride) has been evaluated in eight single dose studies in the mouse and the rat. In these studies doses between 4.5 ml/kg and 36 ml/kg did not produce mortality. The LD_{50} was not established, but is greater than 25 ml/kg (mice) or 36 ml/kg (rat).

In a mouse study, Tyler's Original strain mice were treated with 5.0, 10.0, 20.0 and 25.0 ml/kg Miglyol 812 in a range-finding study with no deaths. In the definitive study conducted with 25 ml/kg, lethargy and ataxia occurred within 10 min after administration of 25 ml/kg, and dyspnoea was noted in some animals within 1 hr, but not thereafter. All animals appeared asymptomatic at the end of the first day. No necropsy observations were reported (Poole, 1977).

Another mouse study tested Miglyol 810 (slightly higher portion of C_8 fatty acids than Miglyol 812) at 12.5, 20.0 and 25.0 ml/kg. Transient ataxia, lethargy, dyspnoea and diuresis occurred within 15 min in the mid- and high-dose groups, and complete loss of activity was observed within 2 hr, followed by recovery, in several animals in the high dose group. Deaths occurred within 24 to 48 hr in two animals that received 20 ml/kg and one animal that received 25 ml MCT/kg. All symptoms disappeared in the survivors by the end of day 3. No necropsy observations were reported (Poole, 1977).

Miglyol 812 was evaluated in fasted Wistar male rats, where a single dose from 4.5 to 36 ml/kg produced no toxic effect during the 10-day observation period or at necropsy. The only observation was

that the animals receiving 18 and 36 ml kg consumed less feed and excreted softer faeces for the first 2 days (Klimmer, 1971).

In each of four single dose acute studies, five male and five female Wistar rats were given 5 g/kg Miglyol 812 and observed for 14 days. No deaths, adverse observations or abnormal gross pathology findings at necropsy were noted (Anonymous, 1977; Lewis and Palanker, 1977; Palanker, 1976a,b).

Acute studies of component fatty acids

Acute toxicological studies have also been carried out in rodents with the constituent medium-chain fatty acids.

A study involving groups of 10 young adult Osborne-Mendel rats established that the oral LD_{50} for caprylic acid was 10,080 mg/kg (Jenner *et al*., 1964). In this study, rats were evenly divided by sex and were fasted for approximately 18 hr prior to treatment by intubation; rats were allowed access to food and water *ad lib* post-treatment. The only indications of toxicity noted by the investigators in surviving animals were depression and diarrhoea.

A study carried out in rats by Smyth *et al* (1962) determined that the oral LD_{50} in rats was 1.41 ml/kg and 3.73 ml kg for caprylic and capric acid, respectively.

The acute toxicity of several mixed preparations of caprylic capric acid triglyceride has also been investigated in a series of oral studies in mice and rats (Elder, 1980). This series of studies indicated that the oral LD_{50} for female mice was greater than 25 ml kg. In the first mouse study, at a dose of 25 ml kg, lethargy and ataxia were observed within 10 min of administration, and dyspnoea within 1 hr. 24 hr after administration, all animals appeared asymptomatic and survival was 100%. In the second mouse study, using doses ranging from 12.5 to 25 ml kg, ataxia, lethargy and dyspnoea were noted within 15 min, which progressed to a complete loss of activity in a few animals by 1 hr. At doses of 20 and 25 ml kg, three deaths out of 15 animals occurred within 48 hr (20% mortality); surviving animals were asymptomatic by 72 hr.

In the same series of oral toxicity studies (Elder, 1980), the oral LD_{50} for male rats was determined to be greater than 36 ml kg. Doses of 18 and 36 ml kg did not result in any mortality and there were no significant findings reported at necropsy on day 14. A second study involving both male and female rats concluded that the LD_{50} of four other mixed preparations of caprylic capric triglyceride was greater than 5000 mg/kg.

Toxicity following dermal administration

No data are available from dermal toxicity tests. However, the observations made during the several studies conducted to assess potential to act as skin sensitizers or to cause dermal irritation (see below) strongly suggest that MCTs are not toxic when administered by the dermal route.

Toxicity following intramuscular administration

In three separate studies, with either five, three or two rabbits, respectively (age and sex not specified), there were no observed muscular reactions, myonecrosis or other toxicologic symptoms following intramuscular administration of 0.5 ml Miglyol 812 (Kracht, 1961, 1962, 1963a).

In two other studies, using three rabbits and two rabbits, respectively (age and sex not specified), 0.5 ml Miglyol was injected intramuscularly six times during a 14-day period. There were no abnormal gross clinical, macroscopic or microscopic pathological findings except for reaction-free oil cysts and localized oil granulomata in the interstitial tissues at the injection site (Kracht, 1961, 1963a).

Toxicity following intraperitoneal administration

In a study with five male Wistar rats per treatment group there were no deaths following administration of single intraperitoneal doses of 1, 2, 4, 8, 16 or 24 ml/kg body weight Miglyol 812. Animals dosed from 8 ml kg body weight upwards showed a diminished appetite and lethargy during the first few days following treatment, possibly due to irritation of the peritoneum caused by dosing. Behaviour returned to normal thereafter. Necropsy at 14 days post-dosing revealed no noteworthy findings except for a residue of test product in the abdomen and slight vascular dilation in the abdominal area associated with delayed absorption of the test material (Klimmer, 1971).

Acute inhalation toxicity

MCT was tested in an acute inhalation study with 10 male Sprague Dawley rats and 10 male Pirbright White guinea pigs that were exposed to an aerosol of undiluted material for 6 hr. The nominal concentration of the MCT (Miglyol 812) in the exposure chamber was 28.1 μl litre air. The fraction of the aerosol with particles small enough to be inhaled (diameter ≤ 5 μm) was 1.97 μl per litre air. One control and three treated animals were sacrificed 1 hr after the exposure period. The remaining two control and seven treated animals of each species were sacrificed 14 days later. All animals were subjected to gross necropsy and microscopic examination of the respiratory tissues.

In rats there were no abnormal general condition or behavioural observations, no differences in body weight or body weight changes in treated animals when compared to the controls, nor any abnormal macroscopic findings in the lungs or trachea. Histopathological examination revealed two treated animals with frequencies of goblet cells of the bronchial mucosa which were very slightly increased over controls. Abnormal histological effects also included one control and two treated rats with very

slightly increased levels of inflammatory infiltration of the stroma. This was described as a chronic, non-specific inflammation. These findings were considered to be insignificant because they were considered to be within the range of normal observations for that species and strain. No other gross or histopathological changes were noted (Reininghaus and Römer, 1977).

In guinea pigs, five treated animals exhibited an increase in goblet cells of the trachea. Small inflammatory, predominately peribronchial, foci were observed in the tracheas of seven treated and one control animal. Four treated guinea pigs exhibited hyperplasia of the basal cells and four animals exhibited squamous cell metaplasia. All observations were ranked as very slight to insignificant because they were considered to be within the range of normal observations for that species and strain. The results of this study indicate that Miglyol 812 should be categorized as practically non-toxic by the inhalation route (Reininghaus and Römer, 1977).

In summary, while no recent acute toxicity studies were found, there is no reason to believe that newer data would affect the conclusion that MCTs and their component fatty acids have a very low acute toxicity in animals, regardless of the route of administration.

Irritation/sensitization tests

Ocular irritation

MCT solutions (10%, 20% and 50%) dissolved in paraffin liquid (DAB 6) were dropped into one eye of each of two human volunteers at 4- to 6-day intervals. An additional five male subjects were tested with undiluted material. No irritation reactions were observed (Potokar, 1971).

Six rabbit eye irritation studies have been conducted to determine whether administering MCT or caprylic capric triglyceride to the eye causes irritation. In one study, instillation of 50 mm^3 (0.05 ml) Miglyol 812 per day for 6 days to the conjunctival membrane of the eyes of three rabbits resulted in no inflammation of the membrane or changes in the cornea during the 10-day observation period (Klimmer, 1971). In five other ocular irritation studies, a single dose of 0.1 ml Miglyol 812 was administered to the eye and observations made for 1–14 days. In four of these studies the compound was considered to be non-irritating (Anonymous, 1977; Busmeier, 1975; Lewis and Palanker, 1977; Palanker, 1976a). In the fifth study (Palanker, 1976b), very mild transient conjunctival redness and discharge of the eye in two of the six rabbits was observed. The test material in the latter study was 50% Miglyol 812 and 50% coconut oil. A summary of the acute rabbit eye irritation studies is presented in Table 2.

Table 2. Summary of acute eye irritation studies with MCT

No. of rabbits	Method, dose, concentration	Times of observation days (hr)	Irritancy score (0–4)	Conclusion	Reference
3	0.05 ml of 50:50 caprylic/capric triglyceride for 6 days	10	0	No tear duct infection or cornea change	Klimmer, 1971
6	0.1 ml, single dose of 50:50 caprylic capric triglyceride, undiluted	1 2 3	0 0 0	No irritation	Lewis and Palanker, 1977
6	0.1 ml, single dose of 50:50 caprylic capric triglyceride, undiluted	1 2 3 4 7	0 0 0 0 0	No irritation	Anonymous, 1977
4	0.1 ml, single dose of 50:50 caprylic capric triglyceride, undiluted	1 2 3	0 0 0	No irritation	Palanker, 1976a
6	0.1 ml, single dose of 50:50 caprylic capric triglyceride in coconut oil	1 2 3 4	0.7 0.3 0.3 0	Very mild transient conjunctival redness and discharge	Palanker, 1976b
6	0.1 ml single dose of 50:50 caprylic capric triglyceride, undiluted	(24) (48) (72)	0 0 0	No irritation	Busmeier, 1975

Dermal irritation

In a dermal irritation study, 40 subjects were patch tested with undiluted MCT. Three readings were made and no skin irritation was noted (Ippen, 1970; Klimmer, 1971).

Dermal irritation capacity was evaluated after application of undiluted MCT (Miglyol 812) to the shaved skin on the backs of rabbits. Following 24, 48 or 72 hr of contact there was no evidence of irritation or inflammation (Klimmer, 1971). MCT was well tolerated in rabbits treated for 2 months in a repeated application cutaneous tolerance test. The test material was categorized as non-irritating (Guillot and Coquet, 1977). However, one sample tested was poorly tolerated and produced a primary irritation index (PII) score of 0.46. This sample caused vesicles to form in three animals, and two of the six biopsies showed pathological intra- and perifollicular retention type inflammation. In three separate tests of a 15% dilution of Miglyol 812 it was shown to be non-irritating (Guillot *et al.*, 1977). Two other samples of MCT were determined to be mildly irritating to the skin when defined erythema and/or oedema was observed in five of six and six of six rabbits, respectively, 24 hr after treatment. The symptoms were not observed at 72 hr after treatment (Busmeier, 1975).

Results of primary skin irritation testing of nine different lots or preparations of MCT (Miglyol 812) are shown in Table 3. The tests reported by Guillot *et al.* (1977) and Guillot and Coquet (1977) were by the Official French government method, while all the remaining tests, except the one reported (Klimmer, 1971) and described above, were by the Draize method. The primary irritation scores show that the samples were non-irritating or were only mildly irritating.

128 adult male and female human volunteers were tested with MCT using a modification of the Draize repeated insult patch test. All subjects had little or no irritation and none was sensitized. One subject had barely perceptible erythema at the first reading immediately following the removal of the first patch which had been applied for 48 hr (Henke and Ede, 1975).

12 women (age not stated) were tested with 0.4 ml MCT applied on a patch. New patches were applied daily to the same site for 21 consecutive days. They were removed 23 hr after application and read at 24 hr. One subject had an erythema score of 1.0 on a scale of 0 to 3 on day 16. The investigators reported that all other scores were 0 and were ranked as negative. This MCT was considered essentially non-irritating for the amount used (Henke and Carabello, 1975).

Sensitization

MCT was tested for potential phototoxic effects on the skin of human volunteers. Miglyol 812 was

Table 3. Summary of primary dermal irritation studies of MCTs in rabbits

No. and sex of rabbits	Concentration[1]	Method	PII[2]	Conclusion	Reference
Unspecified	Undiluted 15%[3]	Occlusive patches "Neodermotest"[5]	0.21 0.08	Non-irritating	Guillot *et al.*, 1977
Unspecified	Undiluted 15%[3]	Occlusive patches "Neodermotest"[5]	0.21 0.00	Non-irritating	Guillot *et al.*, 1977
Unspecified	Undiluted 15%[3]	Occlusive patches "Neodermotest"[5]	0.46 0.04	Non-irritating	Guillot *et al.*, 1977
3 M	Undiluted	Occluded soaked pad 2.5 cm^2 on hair-covered back for 24, 48 and 72 hr	0.00	Non-irritating	Klimmer, 1971
3 M, 3F	Full strength	Draize *et al.*, 0.5 ml, abraded and non-abraded skin, occluded patch, observed at 24 and 72 hr	0.00	Non-irritating	Lewis and Palanker, 1977
6 (sex unspec.)	Full strength	Draize *et al.*, as above	0.25	Mildly irritating	Anonymous, 1977
3 M, 3F	Full strength	Draize *et al.*, as above	0.00	Non-irritating	Palanker, 1976a
3 M, 3F	Full strength[4]	Draize *et al.*, as above	0.05	Non-irritating	Palanker, 1976b
6 (sex unspec.)	Full strength	Draize *et al.*, as above	0.92	Mildly irritating	Busmeier, 1975
6 (sex unspec.)	Full strength	2 months repeated cutaneous application	0.21	Non-irritating	Guillot and Coquet, 1977

[1]Test material was Miglyol 812
[2]PII Primary irritation index
[3]Also contains 3% polyoxyethylene sorbitan stearate (emulsifier), < 2% preservative (not specified) and water to 100%
[4]Approximately 50% caprylic capric triglyceride in coconut oil
[5]Méthod Official de la République Française, 1971 (CTFA, 1986)

applied to the skin and then wiped off after 30 min. Immediately afterwards, the skin surface was divided by horizontal and vertical strips of adhesive plaster into fields approximately 1 cm^2 in area. These fields were exposed to UV light (wavelength not specified) for graduated periods varying from 42 sec to 11.2 min. The skin was examined for changes, especially erythema, after 24 and 48 hr. Examination of the 20 patients noted no skin changes, especially an absence of erythema, after 24 and 48 hr of exposure to light for up to 11.2 min. It was concluded that Miglyol 812 has no phototoxic effect on human skin (Ippen, 1980).

In another study, 100 human patients who had previously displayed various allergic dermatoses, were tested by dermal application of a 1 cm^2 patch of fabric that had been immersed in Miglyol 812. After 48 hr the skin test patches were removed and the treated surfaces were examined for the presence of simple erythema. No evidence of erythema (or other reactions) was noted, confirming that MCTs are unlikely to cross-react in patients with allergic dermatoses of other origin (Degos, 1968; Klimmer, 1971).

A sample of Miglyol 810 was applied to the skin of six guinea pigs as a 4% solution in ethanol with application every other day until 10 applications had been made. Challenge application followed 2 wk after the last induction application. 24 hr after each application readings were made of the erythema and oedema of any skin reactions. No irritation was observed following either the initiation or challenge applications. These results show that Miglyol 810 does not produce sensitization in the guinea pig when applied under these conditions (Anonymous, 1972).

In summary, the results of these studies support the position that MCTs are not dermal or eye irritants. MCTs also are not sensitizers and do not induce photosensitization. Further, these studies support the conclusion that MCTs are not toxic when administered by the dermal route.

Immune function

Some investigators have pointed out that LCT emulsions may impair monocyte, lymphocyte and/or neutrophil functions. These changes seem, however, to be related to quantity and rate of lipid administration. It has been suggested also that emulsions containing predominantly MCTs have less of an adverse effect or no adverse effect at all.

Gogos *et al.* (1990) reported potential differences in the effects on the immune response based on comparisons made with LCT emulsions versus MCT/LCT mixtures. This study included 15 normal subjects, 20 patients receiving glucose-based total parenteral nutrition (TPN), 20 patients receiving LCT-based TPN and 20 patients receiving a 50:50 mixture of MCTs and LCTs. T-lymphocyte subpopulations, including total T cells and T-helper T-suppressor and natural killer (NK) cells and the ratio of helper to suppressor T cells were determined before and 10 days after initiation of TPN. A significant decrease in the ratio of helper to suppressor T cells in the LCT group was found, although no such difference was detected in the MCT–LCT group. No difference was found in total T cells and helper, suppressor or NK cells.

A study was conducted to investigate the immunological effects of three TPN regimens in patients. In the first regimen calories were derived solely from glucose. The other two were identical except that 50% of the calories were provided as an LCT lipid emulsion or as a 50:50 mixture of MCTs and LCTs. NK activity and lymphokine-activated killer (LAK) activity were significantly higher in patients receiving the MCT/LCT solution whereas significantly lower LAK activity occurred in patients receiving the LCT solution. Interleukin 2 content in activated T lymphocyte supernatants was significantly higher in patients receiving the LCT solution. It was suggested that TPN with LCT emulsions or with MCT containing emulsions perturb cytokine interactions; however, the effect is less with MCT containing emulsions and this may augment certain responses (Sedman *et al.*, 1991).

Sedman *et al.* (1990) examined the effects of three lipid MCT- or LCT-based emulsions on IL-2-related interactions *in vitro*. Mitogen-stimulated and IL-2 activated human lymphocyte proliferation were both inhibited in a dose-dependent manner in the presence of all three lipid emulsions. However, the effects were less marked with an emulsion in which half of the calories were derived from MCTs than with a similar emulsion made solely with LCTs. Similarly, the LCT emulsions inhibited the generation of cytotoxic lymphokine-activated killer cells to a greater degree than did the MCT-containing solutions. Neither emulsion inhibited the proliferation of these cell lines, which are not growth factor dependent, but did inhibit the growth of an IL-2-dependent cell line. They concluded that lipid emulsions can upset IL-2-dependent lymphocyte responses. These observations may have relevance for the tumour-bearing patient who is receiving TPN.

The cytotoxic effects against human tumour cells and influence on the immune system of MCTs, LCTs and an MCT/LCT mixture were compared. MCTs showed more potent tumour cell cytotoxicity than did LCTs. Continuous exposure to MCTs also inhibited the cytotoxic effect of LAK cells much more strongly than did exposure to LCTs. However, there is a discrepancy between the concentration of MCT, or the mixture, that could suppress the growth of tumour cells and the concentration that inhibited the cytotoxicity of LAK cells. Moreover, no damage was observed in peripheral blood lymphocytes or LAK cells or in their cytotoxicity when the cells were incubated with triglycerides for 2 hr/day. Thus, short-term

contact with triglycerides could inhibit tumour growth while the immune system was maintained within normal range (Kimoto *et al*., 1998).

The data show, in general, that MCT emulsions may affect lymphokine interactions within the immune system, depending on the emulsion, the regimen and, most likely, the health status of the patient. Certain of these parameters appear to be less adversely affected by MCT emulsions than they are by LCT emulsions although the reasons are not understood at this time.

The toxic potential of MCTs for human bone marrow cells was evaluated in an *in vitro* test system. Bone marrow cells from healthy donors were exposed to emulsions of either LCTs or an MCT/LCT mixture for 24 hr, following which they were cultured for 14 days. Emulsion concentrations ranged from 0 to 10 mg/ml culture medium. Concentrations of 0.5 mg/ml or higher were reported to have significantly inhibited colony formation of the bone marrow cells, as compared to the controls. Effects were reported to be similar for LCTs and the MCT/LCT mixture except for erythroid burst-forming units, which were significantly more inhibited by the LCT emulsion (Beau *et al*., 1997). This study suggests that, for a tissue culture system, moderate to high levels of triglyceride emulsions can adversely affect primary bone marrow cell colonization. Without the metabolic capacity found in intact animals, these triglycerides would be free to affect cell membranes in the *in vitro* model, potentially altering membrane permeability. In the animal and human studies that have been conducted there have been no observations suggesting that triglycerides, including MCTs, have an adverse effects on bone marrow or marrow function.

Studies of the potential to affect the immune response suggest that, under conventional use, MCTs have no effect or may provide enhancement (e.g. IL-2, NK cell, activity) to selective components of the immune system. Under extensive parenteral dosing situations, MCT emulsions may also down-regulate selected immune system functions such as LAK activity.

Subchronic toxicity studies with MCTs

6- to 7-day oral toxicity study in chicks

Miglyol 812 was incorporated into the diet at a level of 16% and fed to 12, 7-day-old Single Comb White Leghorn male chicks for 3 wk. A control group received standard diet. The treated group had reduced body weight gain, ruffled feathers and reduced muscle weight. These effects were due to the reduced feed consumption by chicks receiving the high fat diet. All mortality was due to starvation and not the consumption of Miglyol 812. The absence of "chick oedema factor" was determined by the absence of hydropericardium, hydroperitoneum and subcutaneous oedema at the time of autopsy. Very slight subcutaneous oedema was observed in three treated birds. Heart fluid volume was minimal in all chicks from treated and control birds and there was no evidence of an oedematous condition. Gross autopsy did not reveal any abnormal liver or kidney changes. The results of this study showed that Miglyol 812 did not contain chick oedema factor and that Miglyol is not toxic to chicks (Roth and Shapiro 1981).

30-day oral gavage toxicity study in rats

In two separate tests, groups of 10 male Wistar rats were given either 1 or 3 ml MCT (Miglyol 812) by oral gavage for 30 days. This represented doses ranging from 3.58 to 7.56 ml/kg body weight/day or 10.8 to 21.3 ml/kg body weight/day, respectively, over the course of the studies. No toxic effects or adverse effects on weight gain or urinalysis values were noted, although during the first 5–7 days of the trial there were transitory reductions in food intake and other digestive disturbances, such as diarrhoea (Kimmer 1971).

90-day parenteral toxicity study in rabbits

In a 90-day trial, five rabbits were given 0.5 ml MCT (Miglyol 812) twice a week intramuscularly in the left and right thigh muscles. Two additional rabbits were used as control animals. Histological examination revealed small deposits of oil in the interstitial tissue of the muscle at the injection sites, generally in the form of oil cysts which were enclosed in a non-specific, fibre-rich granulation tissue. These responses were low grade and were considered to be late changes related to the oil cysts which were also described in acute study trials. Miglyol 812 was absorbed and metabolized without any physiological reaction, with the exception of the slight changes due to the initial depot at the injection site and to the injection itself. There were no indications of any changes in the brain, lungs, liver, kidney, spleen, myocardium or hilar lymph nodes. There were no effects on blood measurements of total lipids or total cholesterol when comparing values for the treated and control groups or for the measurements made at the start and end of the study. The results of the study show that Miglyol 812 has good parenteral compatibility in rabbits for both short-term or long-term use (Kracht, 1963b).

3-month oral toxicity study in rats

Groups of 20 male and 20 female rats were fed MCT (Miglyol 812) at 0, 10,000 or 50,000 ppm in the diet (representing 0, 1% and 5% of the diet) for 3 months. There were no reported signs of toxicity and no reported adverse effects on body weight (Table 4), body weight gain, blood chemistry values or organ weights. The blood chemistry included measurements of liver enzymes AST and ALT, and non-esterified fatty acids and esterified fatty acids

Table 4. Mean live body weights (g) of rats fed MCT in the diet for 3 months[1]

Days	Control		10,000 ppm		50,000 ppm	
	Males[2]	Females[2]	Males[2]	Females[2]	Males[2]	Females[2]
0	93 ± 10.4	91 ± 8.1	94 ± 9.7	95 ± 9.6	93 ± 8.8	93 ± 9.3
14	182 ± 20.1	147 ± 8.7	179 ± 17.3	156 ± 12.1	188 ± 14.9	155 ± 12.7
28	243 ± 29.5	178 ± 14.6	239 ± 24.1	189 ± 14.9	250 ± 18.8	187 ± 17.9
42	293 ± 32.4	203 ± 15.4	287 ± 24.3	214 ± 19.3	290 ± 22.7	213 ± 19.5
57	345 ± 35.0	222 ± 18.0	329 ± 26.0	232 ± 23.6	338 ± 23.9	230 ± 19.6
80	375 ± 35.5	237 ± 20.0	366 ± 28.0	248 ± 28.1	376 ± 27.6	244 ± 21.7
94	405 ± 38.4	245 ± 23.6	391 ± 33.0	254 ± 31.7	405 ± 27.3	253 ± 24.2
Percent weight gain days 0–94	+335.5	+169.2	+316.0	+167.4	335.5	+166.5

[1]Values presented as mean ± standard deviation.
[2]n = 20

Table 5. Mean blood chemistry values for rats fed MCT in the diet for 3 months[1]

Measurement	Control		10,000 ppm		50,000 ppm	
	Males	Females	Males	Females	Males	Females
AST mU[2]	64.4 ± 8.16	63.6 ± 5.89	53.0 ± 9.32	59.3 ± 15.02	53.3 ± 10.87	61.2 ± 11.58
ALT mU[2]	14.3 ± 2.98	12.6 ± 3.2	13.7 ± 4.29	12.0 ± 2.9	11.4 ± 2.45	12.1 ± 3.06
NEFA[2] mval/litre	0.59 ± 0.13	0.47 ± 0.22	0.55 ± 0.24	0.46 ± 0.17	0.59 ± 0.21	0.53 ± 0.13
EFA[2] mval/litre	10.0 ± 4.89	3.20 ± 1.67	8.02 ± 3.07	9.87 ± 4.51	7.46 ± 2.06	8.13 ± 3.20

[1]Values presented as mean ± standard deviation; n = 20.
[2]NEFA = non-esterified (free) fatty acids, EFA = esterified fatty acids.

which were all within the normal range (Table 5). This study showed that feeding Miglyol 812 did not increase triglyceride levels or induce a hyperlipidaemic condition. At necropsy, the absolute and brain-weight-relative weights of the liver, kidney, adrenal gland, thyroid gland, gonads and brain of the rats fed the test material were not different from controls (Table 6). The no-observed-adverse-effect level (NOAEL) for this study was determined to be greater than 50,000 ppm in the diet (Klimmer, 1971).

3-month dietary toxicity study in rats

Groups of 25 male and 25 female weanling Crl:CD BR Sprague–Dawley rats were fed caprenin at 0, 5.23, 10.23 or 15.00% in the diet for 91 days. Caprenin is a mixed-chain MCT/LCT consisting of caprylic (23.2%), capric (26.6%) and behenic (C_{22}, 45%) acids. Control animals were fed diets corn oil (12.1%) or a mixture of corn oil and Captex 300, an MCT (3.1% and 11.21%, respectively). All diets contained at least 3% corn oil to provide essential fatty acids and were balanced at about 4000 kcal/kg and provided 26.8% of dietary calories as fat, 19.4% as protein and 52.4% as carbohydrate.

There were no treatment-associated deaths and clinical observations revealed no findings that were uncommon or at increased frequency for animals of this type and age, with the exception of increased incidences of tail desquamation in animals on the corn oil/MCT diet. There were no significant differ

Table 6. Mean absolute organ weights and brain-weight-relative organ weights (g) for rats fed MCT in the diet for 3 months[1]

Organ	Control		10,000 ppm		50,000 ppm	
	Males	Females	Males	Females	Males	Females
Terminal body weight	402 ± 43.5	241 ± 25.1	390 ± 32.5	254 ± 31.0	403 ± 33.6	253 ± 27.4
Mean absolute organ weight						
Liver	15.225 ± 2.5164	8.747 ± 0.8333	13.762 ± 1.7297	9.383 ± 2.7653	14.901 ± 1.6400	9.681 ± 0.9853
Kidney	2.518 ± 0.3418	1.511 ± 0.1563	2.492 ± 0.2214	1.582 ± 0.2076	2.572 ± 0.3385	1.866 ± 0.2108
Adrenal	0.055 ± 0.0103	0.070 ± 0.0126	0.064 ± 0.0077	0.075 ± 0.0092	0.056 ± 0.0053	0.087 ± 0.0072
Thyroid	0.0167 ± 0.00422	0.0139 ± 0.00311	0.0224 ± 0.00484	0.0160 ± 0.00403	0.0178 ± 0.00365	0.0165 ± 0.00350
Gonads	4.422 ± 0.4660	0.103 ± 0.0150	4.541 ± 0.3443	0.101 ± 0.0138	4.606 ± 0.4289	0.113 ± 0.0226
Brain	1.913 ± 0.1780	1.689 ± 0.1624	1.924 ± 0.1171	1.808 ± 0.1273	1.982 ± 0.0578	1.823 ± 0.0798
Brain weight relative organ weights						
Liver	7.976 ± 1.144	5.202 ± 0.539	7.188 ± 1.122	5.213 ± 1.026	7.465 ± 0.767	5.120 ± 0.55
Kidney	1.319 ± 0.154	1.018 ± 0.103	1.303 ± 0.176	0.990 ± 0.134	1.297 ± 0.157	1.025 ± 0.123
Adrenal	0.029 ± 0.006	0.042 ± 0.009	0.033 ± 0.004	0.043 ± 0.006	0.028 ± 0.003	0.048 ± 0.004
Thyroid	0.009 ± 0.002	0.008 ± 0.002	0.012 ± 0.003	0.009 ± 0.002	0.009 ± 0.002	0.009 ± 0.002
Gonads	2.323 ± 0.263	0.061 ± 0.009	2.373 ± 0.301	0.056 ± 0.009	2.323 ± 0.284	0.063 ± 0.014

[1]Values presented as mean ± standard deviation, n = 10

ences in body weights or body weight gains across all groups. In the groups fed caprenin, male rats exhibited lower liver-to-body weight ratios and females exhibited lower absolute liver weights, both of these observations were attributed to reduced deposition of fat in the livers. Males on the 15.0% caprenin diet consumed significantly more feed and females consumed significantly less feed than the corn oil or corn oil MCT dietary groups. Differences in haematologic and clinical chemistry values across all groups were considered to be not toxicologically significant, approximating historical control values, and were not related to treatment. Necropsy evaluation included granular pitted rough renal observations for high-dose caprenin diet fed females; however, this observation had no histopathological correlate and was considered to be related to renal changes (nephrocalcinosis) that occur normally in female rats. There were no other gross or histopathological findings reported. There were no significant differences among groups in the total fat content, as weight percent, of the hearts, livers or perirenal fat pads, however, there was a trend to lower amounts of fat deposited in the livers of animals fed caprenin-containing diets. The NOAEL for caprenin was determined to be equal to or greater than 15% of the diet (13.2 and 14.6 gm/kg body weight/day for males and females, respectively) and for MCTs, in the corn oil MCT diet, to be greater than 11.2% of the diet (approx. 9.2 gm/kg body weight/day) (Webb *et al.*, 1993).

Subchronic dietary studies with MCTs and LCTs

Many of the subchronic studies that have been carried out with MCTs in laboratory animals and in humans were designed to compare MCT- with LCT-containing diets. In the accounts of these studies the effect of an MCT-based diet on an endpoint of interest (e.g. degree of fat deposition) is reported relative to the effect or response observed after feeding an LCT-based diet.

Rat studies

No significant adverse effects were observed in a study wherein 15 male Sprague-Dawley rats were fed, via oral intubation, either an MCT- or LCT-containing diet which derived 50% of the calories from fat for 6 weeks. Animals fed the MCT diet had significantly lower levels of dissectable fat, which was attributed to higher resting and maximal norepinephrine-stimulated O_2 consumption and metabolic rate. Liver fat and blood glucose values were comparable between the two groups (Baba *et al.*, 1982).

In a similar study in which male Sprague-Dawley rats were fed, via oral intubation, an MCT or LCT diet which derived 50% of the calories from fat, for 6 wks. MCT-fed rats gained 20% less weight and had fat depots weighing 23% less than LCT-fed rats. During wk 6 of the study, rats were monitored for total spontaneous physical activity over a 24-hr period and no differences between the two groups were noted, suggesting that MCTs do not induce overt toxicity as would be suggested by the absence of lethargy. Serum insulin levels and the weights of carcass protein and water were not different between the two groups (Oscilbitz *et al.*, 1983).

Another study used male Wistar CF rats which were fed fat-containing diets for 45 days in which 32% of the metabolizable energy was constituted by LCTs or MCTs. The data showed that rats fed the MCT diet had depressed levels of serum cholesterol, weight gain was decreased by 21% and energy retention was decreased by 26% relative to the LCT-fed rats. The LCT diet increased lipid deposition 1.5-1.7-fold. No significant differences were noted between the LCT and MCT groups with respect to plasma glucose, triglycerides, free fatty acids or liver weight; hepatic glycogen levels were 50% lower in the LCT group (Chanez *et al.*, 1991).

Human studies

A study was conducted with cystic patients who were fed formula diets containing either MCTs [77.7% C_8 (caprylic), 19.6% C_{10} (capric), 1.9% C_6 and 0.8% C_{12}], butter or corn oil as the sole isocaloric source of dietary fat. The study lasted up to 10 wk and used a crossover study design; each formula derived 40% of its caloric content from fat. The MCT- and corn oil-containing diets were shown to produce significantly lower cholesterol levels, relative to steady-state levels achieved on the butter diet. The only side-effect documented for the MCT formula was a transient period of nausea and abdominal fullness during the first 3-4 days (Hashim *et al.*, 1960).

Four human volunteers who had fasted overnight were fed 1 g MCT/kg body weight [71% caprylic, 25% capric, 3% lauric]. Their serum-free fatty acids showed a high proportion of octanoic acid and a low proportion of long-chain acids for 4 hr after feeding the MCT preparation. No toxicologic symptoms were reported (CTFA, 1980).

When 10 human volunteers ingested 100 ml (approx. 95 g) of synthetic fat (a triglyceride of 74% lauric, 17% capric, 5% caprylic, 3% myristic, and a trace of caproic), eight had no chylomicrons in their sera and none developed diarrhoea or had fat in their faeces. All had increased levels of free fatty acids in their sera. These results support other data which show that MCTs are readily metabolized in the intestine and are absorbed primarily as free fatty acids without adverse effects (CTFA, 1980).

In another study, 10 non-obese males were overfed (150% of estimated energy requirements) two formula diets for 6 days each, in a randomized crossover design. The fat component of the diets represented 40% of caloric energy either as MCT or LCT. No significant clinical toxicity was

reported. In contrast to the reports cited above, a reduction in fasting serum total cholesterol was noted for the LCT diet but not for the MCT diet. A threefold increase in fasting serum triglyceride values was noted for the MCT, but not for the LCT diet. It was suggested that MCT diets, when fed in excess of caloric needs, might lead to increased *de novo* fatty acid synthesis and enhanced fatty acid elongation activity in the liver (Hill *et al.*, 1990).

In summary, the more recent subchronic studies provide confirmation of earlier dietary or parenteral treatment studies and the outcome of such studies appear to be consistent over time. The MCTs exhibit very low toxicity when administered in the diet at levels up to 15% of the diet. MCT-based diets have been shown to cause minor alterations in serum lipid profiles, which have occasionally translated into slower rates of weight gain relative to LCT-based diets. There is an apparent debate on the effect of an MCT-based diet on serum cholesterol levels. This appears to relate to the dietary comparisons being made. Compared to a high butterfat diet (Hashim *et al.*, 1960), cholesterol levels were decreased, but compared to a high LCT diet (Hill *et al.*, 1990), cholesterol levels were not decreased. None the less, the subchronic studies in both animals and man have indicated that MCT-based diets do not cause significant toxicity to humans or to laboratory animals.

Developmental and reproductive toxicity studies

In a study with Sherman albino rats that were fed diets containing 20% of either lard or MCT in addition to 0.09% linoleic acid for 10–12 months, no effect on fertility was noted. When treated male rats were mated at 9 months of age with control females, all males were found to be equally fertile and litters were normal with respect to number and weight. When female rats which had been maintained on the MCT diet supplemented with either 0.09 or 2.0% linoleic acid were mated with males that had been treated with the MCT diet + 0.09% linoleic acid, normal litters occurred. However, the lactation performance of females on MCT diets supplemented with 0.09% linoleic acid was reported as being poor, as evidenced by lower survival and growth rates of their offspring. The second litter pups from females who had been maintained on the MCT + 0.09% linoleic acid diet were then in turn maintained on MCT + 0, 0.09 or 2% linoleic acid. Half of the males on the 0% linoleic supplement died, however, all survivors and all rats of the other groups grew to weights which correlated with the amount of linoleic acid given. The second-generation animals initially showed signs of linoleic acid deficiency, but these symptoms eventually resolved without the addition of linoleic acid supplements. Thus, while dietary levels of linoleic acid affected offspring growth and survival parameters, the incorporation of 20% MCT had no adverse effects on reproduction (Kaunitz *et al.*, 1958).

In a reproductive toxicity study, young adult male and female Wistar rats were fed a balanced diet containing 19.6% of an MCT of 75% caprylic and 25% capric acid for 3 wk before mating. This group was compared to concurrent groups fed high oleo oil, butter fat or coconut oil diets. Body weight gain and litter size and birth weights of the animals on the MCT diet were similar to those of rats on the other diets. Mortality of the F_1 and F_2 pups during lactation was somewhat higher, and weight gain was slightly lower in the MCT diet group pups. This was directly attributed to a smaller volume of milk secreted by the dams and was supported by observations that there was considerably less body fat on these animals. After weaning, the F_1 and F_2 generations, which continued to be fed the MCT diet, showed a weight gain comparable to that of control rats on the other diets. There were no adverse effects on reproductive parameters or on pup development aside from slightly lower body weight gains during the lactation period (Harkins and Sarett, 1968).

Two developmental toxicity studies were carried out, in parallel, with 25 pregnant female Crl:CD rats and 15 pregnant female HRa. (NZW) SPF rabbits administered a 3:1 mixture of MCT and LCT during the period of organogenesis. Test material administration was via intravenous infusion (tail vein in rats, ear vein in rabbits) of either 0, 1.0 or 4.28 g lipid/kg body weight/day. Female rats were sacrificed and necropsied on day 20 and female rabbits were sacrificed on day 29 of gestation. Ovaries were examined and the number of corpora lutea was recorded. The uteri were removed from each rat and weighed, and the number and placement of implantation sites (live and dead foetuses, and early and late resorptions) were recorded. Foetuses were removed, weighed and examined for external, soft tissue and skeletal abnormalities.

There were no test material-related deaths in either trial. There were no adverse effects of treatment in rats or rabbits administered 1.0 g lipid/kg body weight/day and there were no adverse effects of treatment on the foetal parameters.

Rats that received 4.28 g lipid/kg body weight/day exhibited a non-significant trend towards reduced feed consumption during treatment, tail lesions associated with extravasation of the test article, enlarged lymph nodes, spleens and renal pelvises and small thymuses. There were no statistically significant adverse effects on foetal parameters. The NOAEL for maternal toxicity in rats was equal to or greater than 4.28 g/kg body weight/day (3.21 g MCT/kg body weight/day) and the NOAEL for foetal toxicity and other foetal effects was equal to or greater than 4.28 g/kg body weight/day.

Rabbits that received 4.28 g/kg body weight/day exhibited statistically significantly reduced feed con-

sumption, statistically significant body weight loss and faecal output during treatment. Enlarged lymph nodes, spleens and renal pelvises and small thymuses were also observed. Statistically significant effects observed in foetuses included foetal toxicity, evidenced by increased incidences of resorptions (post-implantation loss of 17.1% *vs* 2.3% in the controls), lower body weights (76% of control values). Increased incidences of skeletal anomalies, including unossified skull bones, misaligned sternebrae, presacral vertebrae and fused ribs were noted, but were determined not to be statistically significant when compared to controls. These foetal effects were attributed to the dietary deprivation of the dams during the treatment period. The NOAELs for maternal toxicity and for foetal toxicity in rabbits were both greater than 1.0 g/kg body weight/day and less than 4.28 g/kg body weight/day (Henwood *et al.*, 1997; Wilson *et al.*, 1996).

An experiment was conducted to determine whether feeding MCTs to sows during late gestation (G) and early lactation (L) would improve neonatal pig survival. Beginning on day 91G and continuing through day 7L, sows were fed isoenergetic (7000 kcal metabolizable energy/day) and isonitrogenous (2.8 g crude protein/day) amounts of either control (9% starch, 2% soybean oil), long-chain triglycerides (LCT, soybean oil, 12%), or MCT (10% MCT, 2% soybean oil) diets. Sows (*n* = 18, 19 and 17, respectively) were induced to farrow on day 112G. Litters were weighed at birth, before suckling, and on days 1, 3, 7 and 21L. There was no effect of treatment on average pig weight at any time and no difference in the number of live pigs at birth. Beginning on day 3L ($P < 0.05$) and continuing through weaning (day 21L, $P < 0.02$), survival was improved in litters from sows fed MCT relative to litters from sows fed the control diet. Overall survival rates were 80, 81 and 90% in control, LCT and MCT groups, respectively. The greatest improvement in survival was observed in pigs weighing less than 900 g at birth. Survival of pigs in this weight range was 32, 53 and 68% in control, LCT and MCT treatment groups, respectively. Although feeding MCT resulted in an increase in content of MCFAs in milk, these accounted for less than 1% of the fatty acids in milk and likely cannot account for the improved survival rate. The observation of increased blood glucose ($P < 0.05$) at birth in pigs from both the LCT- and MCT-fed sows is supportive of a prenatal effect of the diets. The results suggest that not only is survival improved, but that certain reproductive parameters, such as litter size, live births, birth weights and litter survival during early lactation and late lactation, are not adversely affected by dietary administration of MCTs (Azain, 1993).

In summary, MCTs administered in the diet or by the intravenous route had no adverse effect on rat reproductive or developmental parameters. MCTs administered in the diet had no adverse effect on terminal gestational development and postnatal survival of pigs. In contrast, MCTs infused intravenously in rabbits over a daily 4-hr period at a level of 4.28 g/kg body weight caused a loss in body weight in dams and developmental toxicity in the pups from those dams. However, this effect may be attributed to dietary deprivation of the dams, especially in view of the absence of a similar effect in a parallel intravenous treatment study in rats. The newer studies affirm older data which show that MCTs are not reproductive or developmental toxicants.

Chronic toxicity/carcinogenicity studies

In a study in which Sherman albino rats were fed diets containing 20% of either lard or MCT in addition to 0.09% linoleic acid for 10 to 12 months, no overt toxicity was observed and there was no difference in survival between the two groups. Rats fed MCT gained approximately 15% less weight during the study. This difference was shown not to be the result of faecal fat losses. A second component of the study involved the comparison of serum cholesterol levels in rats fed the lard-based diet *vs* the MCT-based diet supplemented with either 0, 0.09 or 2% linoleic acid. Rats fed the MCT diet had serum cholesterol levels which ranged from 55 to 76 mg% *vs* 83 to 129 mg% for rats on the lard diet. The rats fed diets with 0.09% linoleic exhibited greater caloric requirements than the groups fed diets containing 2.0% linoleic acid or lard. There were no adverse toxicological effects reported for animals fed diets containing MCT (Kaunitz *et al.*, 1958).

The chronic toxicity profile of MCTs was evaluated in a dietary study involving 25 male and 25 female Wistar rats. The rats were fed diets that differed only with respect to the source of the dietary fat that supplied 40% of the total calories (21% fat). The fats tested were MCT (approx. 75% caprylic and 25% capric), oleo oil, butter fat and coconut oil to which 2.5% safflower oil was added to ensure adequacy of the essential fatty acids in all diets. The study period was 47 wk. The consumption of MCT was approximately 9 g/kg body weight/day. The results showed that the MCT diet supported normal growth and development and there was no difference in mortality between the various treatment groups. Organ weights of the liver, kidney, spleen, heart, adrenals, and testes were similar in all groups at the end of the study, and histological examination of the liver and intestine showed no marked differences. At the end of 47 wk, mean weight gain for rats fed the MCT diet was equivalent to those recorded for all other diets, but significantly less than that observed in rats fed the coconut oil based diet (Harkin and Sureti, 1968).

The US National Toxicology Program (NTP) tested tricaprylin, a triglyceride in which all three fatty acids are C_8, caprylic acid) in a 2-yr chronic toxicity and carcinogenicity study. In this study, male F344/N rats were gavaged with 0, 2.5, 5 or 10 ml tricaprylin/kg body weight daily, 5 days per week for 2 yr.

The 2-yr survival of high-dose tricaprylin male rats was lower than that of the control rats (0 ml/kg 31/50; 2.5 ml/kg 30/50; 5 ml/kg 31/50; 10 ml/kg 23/53) due to moribund kills and deaths that appeared to be related to toxicity. The mean body weight of the high-dose group was lower than that of the controls throughout the study, although the difference was less than 5% after wk 61.

There were significant dose-related increased incidences of pancreatic exocrine hyperplasia and adenoma (hyperplasia: 8/49, 9/49, 18/49, 28/50; adenoma, 2/49, 6/49, 13/49, 18/50 in the 0, 2.5, 5 and 10 ml/kg groups, respectively). The incidence of proliferative lesions of the forestomach increased significantly with dose (basal cell hyperplasia: 4/50, 7/50, 12/49, 21/52; squamous cell papilloma: 0/50, 0/50, 3/50, 10/53). The incidence of nephropathy was significantly decreased in high-dose rats, and the severity of nephropathy decreased with increasing dose [incidence (mean severity grade): 46/50 (2.0), 42/50 (1.5), 45/50 (1.7), 27/49 (0.9)]. In high-dose group rats, the incidence of mononuclear cell leukaemia was decreased (23/50, 28/50, 22/50, 9/53). There were no significant increases in carcinomas found in this study.

Although the study report did not identify a toxicity NOAEL, it appears that there would not be a statistically significant difference in any of the observed parameters between untreated control and 2.5 ml/kg groups. Therefore, the toxicity NOAEL for tricaprylin would be 2.5 ml/kg body weight/day or about 2.37 g/kg body weight/day (NTP, 1994).

In contrast to the NTP study and to other chronic studies cited above, it has been suggested, in one report, that tricaprylin may act to facilitate tumour cell metastasis. In this study, rats were injected with ACL-15 tumour cells via the portal vein, then were placed on three sources of TPN. TPN consisted of tricaprylin as an MCT or soybean oil as an LCT or dextrose. These components comprised 50%, 50% and 100% of non-protein calories, respectively. Evaluation of liver surface metastases showed more surface metastases in rats that had been treated for 2 or 11 days with MCT following tumour cell inoculation (Ohkawa *et al.*, 1997). This finding is difficult to interpret in view of the absence of increased incidences of tumours in the other studies cited, and in view of the fact that the livers of these rats were experimentally implanted with tumour cells. The effects of reduced caloric intake on the evolution of spontaneous tumours and on survival is the subject of study by NTP and other laboratories (Dixit and Kacew, 1997; Giknis and Clifford, 1998; Hoberman *et al.*, 1996; Kari and Abdo, 1997). Caloric restriction can be achieved, among other means, by reduction of dietary fat levels to less than 5%. It is established that doing so will result in increased survival and reduction of tumour incidences, especially endocrine-mediated tumours. The reverse phenomenon, of increased dietary calories/fat leading to increased spontaneous tumour incidences, has not been conclusively established. The capacity of tricaprylin to promote tumour metastases needs to be evaluated in other less invasive and more naturally occurring experimental scenarios.

In summary, chronic studies in F344/N rats involving oral gavage of the MCT tricaprylin for 2 yr showed an increase in mortality at 10 ml/kg body weight/day (approx. 9.5 g/kg body weight/day). This was accompanied by observations of increased incidences of pancreatic and forestomach hyperplasia and adenoma, but not carcinomas, at 5 and 10 ml/kg. In contrast, no significant toxic effects or effects on mortality were noted in Wistar rats or Sherman rats fed mixed-chain MCT in the diet for 1 yr at levels up to 20% of the diet (about 10 g/kg body weight/day). None of the effects seen in the subchronic studies suggests a carcinogenic potential for MCTs. Therefore, the results of the chronic studies are consistent with the findings of the acute and subchronic studies and suggest that MCTs have very low toxicity. These studies also suggest that the route of administration (dietary inclusion *vs* oral gavage) may influence the apparent toxicity of MCTs during chronic administration.

Genotoxicity/mutagenicity studies

Caprylic acid exhibited no mutagenic activity in microbial mutation assays with and without metabolic activation. The indicator organisms were *Saccharomyces cerevisiae* strain D4 and *Salmonella typhimurium* strains TA1535, TA1537 and TA1538 (Brusick, 1976).

Tricaprylin was tested for mutagenic activity in the Ames mutagenicity plate incorporation assays with and without metabolic activation in conjunction with the NTP chronic toxicity study. Tricaprylin was mutagenic in strain TA1535 with but not without S9. Tricaprylin did not induce mutations in strains TA97, TA98 or TA100, with or without S9 (NTP, 1994).

In summary, the evidence for the genotoxicity of MCTs is weak. Tricaprylin was not classified as a carcinogen in the chronic carcinogenicity study and caprylic acid was not mutagenic in yeast or bacteria. The positive result with tricaprylin in one strain of bacteria in the Ames test, does not appear to suggest that tricaprylin should be classified as a mutagen. Additional data in other *in vitro* or *in vivo* genotoxicity assays could confirm this assumption.

Special considerations with regard to oral administration of MCTs

Discussion of potential ketosis effects

MCTs are hydrolysed to MCFAs in the intestinal lumen, absorbed and transported to the liver via the portal vein. The hepatic mitochondrial metabolism of MCFAs such as caprylic and capric acid ultimately results in an excess of acetyl-CoA, which in turn results in the production of acetate, CO_2 and ketone bodies, with a minor portion being utilized to lengthen endogenous fatty acids (Bach and Babayan, 1982). The production of ketone bodies such as β-hydroxybutyrate in the liver can lead to an elevation of the β-hydroxybutyrate serum concentrations. This has been documented in a number of papers, some of which are summarized below, followed by an interpretive summary of the clinical significance of these findings.

Animal studies

The effect of MCT and LCT ingestion on ketonaemia was investigated in Wistar rats after a single oral dose of 1.5 g of either fat; control rats were treated with NaCl. Blood samples were obtained throughout the first 100 min after fat ingestion. Blood analyses suggested that the level of ketone bodies, β-hydroxybutyrate and acetoacetate in the blood did not vary after LCT treatment, but were significantly increased after the administration of MCT. β-hydroxybutyrate levels reached a peak approximately 15 min after MCT ingestion, at which time blood levels reached approximately 700 nmol/ml and were approximately fivefold higher than those of the rats in the LCT and control groups (Bach *et al.*, 1977).

Male Wistar CF rats were fed fat-containing diets in which 32% of the metabolizable energy consisted of LCTs or of MCTs. Feeding was carried out for a period of 45 days. Blood ketone body concentrations in the MCT-fed rats were significantly greater than LCT-fed rats only on day 1, but were comparable on days 4, 8, 15, 25 and 45. The mean blood ketone body values on day 1 in the MCT group were approximately 100 nmol/ml blood (Chance *et al.*, 1991).

An evaluation of the literature regarding the effects of dietary MCTs on diabetic rats provides support for the conclusion that there is no risk of ketoacidosis or ketonaemia with MCTs. Edens and Friedman (1984) reported a study wherein normal and diabetic rats were fed diets with increasing levels (5% to 15% to 25%) of either corn oil (LCT) or MCT. It was reported that caloric intake was more rapidly adjusted in the normal and diabetic rats fed the MCT-containing diet. Plasma triglycerides and glycerol were decreased in both normal and diabetic rats fed the MCT-containing diet. However, plasma ketones in the normal rats were increased whereas there was no apparent effect on plasma ketones in the diabetic rats.

A comparative study of the effects of administration of emulsions containing an MCT/LCT mixture or LCT alone on plasma lipids and nitrogen retention was conducted in normal and streptozotocin-induced diabetic rats (Chen *et al.*, 1997). Rats were placed on total parenteral nutrition with solutions providing 37.5% of the non-protein energy as fat. Fat consisted of either LCT or a 1:1 mixture of MCT/LCT. The results showed that, in diabetic rats, plasma triacylglycerol, non-esterified fatty acids (NEFA), and β-hydroxybutyrate levels were higher compared to control rats, whereas plasma insulin levels and nitrogen retention were lower. Following TPN administration, plasma glucose levels, triacylglycerol, non-esterified fatty acids and β-hydroxybutyrate levels were significantly decreased in diabetic groups. However, plasma glucose and triacylglycerol levels remained higher than in control animals. No differences in the concentrations of plasma triacylglycerol, cholesterol, non-esterified fatty acids, β-hydroxybutyrate or nitrogen retention were observed between the two diabetic groups. These results suggest that MCT/LCT infusion did not lead to hyperketonaemia and hypercholesterolaemia as compared with LCT infusion, and had no beneficial effect on nitrogen retention in rats with streptozotocin-induced diabetes under these experimental conditions.

These model studies in rats provide confirmation of the absence of risk of ketoacidosis or ketonemia in humans with dietary MCTs.

Human studies

10 male volunteers were overfed (150% of estimated energy requirement) liquid formula diets containing 40% fat as either MCT or LCT; each patient was studied for 1 wk on each diet in a cross-over design. Overfeeding with the MCT diet produced higher fasting serum levels of β-hydroxybutyrate on day 6 relative to the LCT diet. After the meal on day 6, β-hydroxybutyrate levels increased during the postprandial period in the MCT group, whereas levels in the LCT group did not change. At 1 hr after the meal on day 6, β-hydroxybutyrate serum levels were approximately 180 nmol/ml and at 3 hr were approximately 300 nmol/ml (Hill *et al.*, 1989).

The ketogenic effects of MCTs are more pronounced in diabetics than in healthy subjects (Bach and Babayan, 1982). A study was conducted with five healthy and three insulin-dependent diabetic volunteers; each volunteer received an oral dose of 10–75 ml MCT after an overnight fast. Alveolar acetone concentrations, measured over the following 12–18 hr, were shown to increase relative to the volume of MCT ingested, but not in a linear fashion. The mean ketogenic response to MCT of three insulin-dependent diabetic patients was ap-

proximately 2.5 times greater than that for the four healthy volunteers after an ingestion of 25 ml MCT. After a dose of 30 ml MCT, peak acetone levels (approx. 1.0 μg acetone/100 ml alveolar air) were observed at 6 hours. Acetone production could be antagonized by the concomitant ingestion of sucrose. It was suggested, from the results, that the magnitude of ketosis is the result of carbohydrate deficiency relative to the amount of fat entering the liver. This study showed that the ingestion of MCT results in an increase in acetone production in end-expiratory air; acetone levels were assumed to reflect the ketogenic effect of MCTs. The acetone concentrations were not converted to serum ketone equivalents, however, and thus they cannot be compared to the ketone body levels cited in the studies above, or to the levels associated with diabetic ketoacidosis. Therefore, although increased levels of acetone were found in the MCT-fed diabetic volunteers, it cannot be determined from this study, whether there is cause for concern with respect to the consumption of MCTs by insulin-dependent diabetics (Freund and Weinster, 1966).

Normal circulating ketone body concentrations in the fed state are approximately 100 nmol/ml, but can be as high as 2000–3000 nmol/ml in individuals on high protein, carbohydrate-free diets (Shils *et al.*, 1994). The blood levels of ketone bodies in investigations cited above were in the normal range, 100–700 nmol/ml, yet are at least 10-fold lower than levels associated with diabetic ketoacidosis which are in the range of 8000–15,000 nmol/ml (Gornall, 1981). If the ketogenic response of an insulin-dependent diabetic patient is 2.5 times greater than that of non-diabetics (Freund and Weinster, 1966), and if an MCT-based diet results in maximal blood ketone bodies of 300 nmol/ml in non-diabetic patients (Hill *et al.*, 1989), then blood ketone levels in diabetics on the same diet used in the study described above (Hill *et al.*, 1989) would not be expected to exceed 750 nmol/ml. It can be argued, therefore, that the risk of MCT-induced ketoacidosis would be negligible in healthy individuals and in Type II diabetic patients. MCTs would be only mildly ketogenic in Type I diabetic patients, who are normally on controlled diets, thus ingestion of appropriate amounts of fat might limit the risk even further (Fischer, 1991). Similarly, it was acknowledged (Bach *et al.*, 1989) that although MCTs can lead to ketone production, there is no risk of ketoacidosis or ketonaemia with MCTs.

Discussion of a special population—persons with cirrhosis or liver disease

Fat malabsorption sufficient to contribute to malnutrition is common in cirrhosis (Linscheer *et al.*, 1966). In a clinical study designed to evaluate the incidence of fat malabsorption in patients with alcoholic cirrhosis, a group of 10 patients was given equicaloric MCT or LCT liquid diets in alternating periods of 6 days. The absorption of MCTs was found to be significantly better than of LCTs, as determined from stool fat measurements. In the same study, the absorption of caprylic acid after infusion into the upper small bowel was compared between control and cirrhotic patients. An analysis of plasma caprylic acid concentrations demonstrated that although there were comparable rates of absorption between the two groups, plasma concentrations of caprylic acid were two- to threefold higher in the cirrhotic patients, immediately after the 60-min infusion period. This suggested that the capacity of cirrhotic livers to clear absorbed caprylic acid and presumably other MCFAs, is compromised.

A subsequent study (Linscheer *et al.*, 1970), in which control and cirrhotic patients were administered a test meal of MCTs (0.5 g per kg lean body mass), also showed that serum concentrations of caprylic acid were approximately twofold higher in the cirrhotic group. Furthermore, it was shown that caprylic acid concentrations were four- to fivefold higher in the spinal fluid of cirrhotic patients.

As described above, MCTs are absorbed and transported directly to the liver, where they are metabolized; thus, only a small fraction of free MCFAs reach the general circulation in the presence of normal hepatic function. In the presence of liver disease such as cirrhosis, the capacity of the liver can be significantly compromised, resulting in decreased clearance of caprylic acid in addition to a decreased production of albumin (Bach and Babayan, 1982). Although it has been demonstrated that cirrhotic patients have elevated blood and spinal fluid levels of caprylic acid following MCT ingestion (Linscheer *et al.*, 1966, 1970) it has not been demonstrated that this is a causative factor in CNS effects described as hepatic encephalopathy (Johnson and Cotter, 1986; McCandless, 1985).

Central nervous system effects

Animal studies have been carried out to investigate the potential CNS effects of the administration of high doses of caprylic acid.

The intraperitoneal administration of caprylic acid can induce coma in mice. At a dose of 15 μmol/g (2160 mg/kg), mice exhibited a transient period of drowsiness followed by coma. The mechanism underlying the resulting coma was shown to be the result of a selective effect on energy metabolism within cells of the reticular formation. These changes consisted of a decrease in ATP and phosphocreatine and an elevation of glucose and glycogen (McCandless, 1985).

MCTs can also cause CNS toxicity after intravenous administration in dogs. A study was carried out in dogs that were infused with trioctanoin (caprylic acid), after a 12-hr fast, at rates which increased in a stepwise fashion from 26 to 35 to 44 μmol/kg·min, with each infusion lasting for

80 min. These doses correspond to total doses of 1.15, 1.55 and 1.95 g/kg, respectively. No signs of toxicity were noted at the lowest infusion rate, but at the two higher rates hypotonia and somnolence were noted, followed by unconsciousness and repeated emesis in some animals. The infusion resulted in plasma concentrations of ketone bodies of 423, 756 and 859 nmol/ml at 80, 160 and 240 min; basal levels were 102 nmol/ml. These changes were accompanied by increases in plasma lactate, as well as electroencephalographic changes. Plasma octanoate concentrations ranged from 250 to 1500 nmol/ml (Miles *et al.*, 1991).

In rats, mice, dogs, guinea pigs and monkeys, CNS effects require blood concentrations of octanoate of approximately 3–8 μmol/ml (Johnson and Cotter, 1986). The effect of intravenous sodium octanoate in rhesus monkeys was investigated. Infusions at doses of 5 mM/kg for 20 min produced clinical and electroencephalographic syndrome comparable to hepatic encephalopathy. The serum concentrations of sodium octanoate that were achieved in this experiment were described as many times higher than those observed in comatose cirrhotic patients which are in the range of 10 to 18 mEq/litre (10–18 nmol/ml) (Rabinowitz *et al.*, 1978).

In summary, MCTs are catabolized and absorbed more efficiently than LCTs. In patients with cirrhosis of the liver, MCTs are capable of providing a significant source of calories. Cirrhosis-induced hepatic dysfunction also results in a decrease in the hepatic clearance of caprylic acid, which can lead to elevated levels of caprylic acid in the serum and in the spinal fluid. It is not known whether this is a causative factor in hepatic encephalopathy. Unesterified caprylic acid is capable of producing CNS toxicity in animal models comparable to that of clinical hepatic encephalopathy, but this was only achieved at serum caprylic acid concentrations 166- to 800-fold higher than those observed in patients with hepatic encephalopathy. In these studies the intravenous or intraperitoneal routes of administration are unrelated to the likely oral route of exposure in cirrhotic persons. Therefore it is unlikely that high circulating levels of caprylic acid alone are responsible for the development of hepatic encephalopathy in cirrhosis patients. It also appears highly unlikely that the consumption of MCTs in the diet would pose any concern for neurological effects as a result of the metabolic release of caprylic acid.

Overall summary

MCTs are essentially non-toxic in the acute toxicity tests conducted in several species of animals. In ocular and dermal irritation testing, MCTs exhibited virtually no potential as ocular or dermal irritants, even with prolonged eye or skin exposure. MCTs exhibit no capacity for induction of hypersensitivity. 90-day toxicity tests did not result in notable toxicity, whether the product was administered in the diet up to 9375 mg/kg body weight/day in rats or by intramuscular injection (up to 0.5 ml/kg/day, rabbits). The toxicity NOAELs for two 3-month feeding studies in rats were, respectively, equal to or greater than 3125 mg/kg body weight/day and equal to or greater than 9375 mg/kg body weight/day in the diet. There was no evidence that dietary administration of MCTs adversely affected the reproductive performance of rats or resulted in maternal toxicity, foetal toxicity or teratogenic effects at doses up to 4.28 g/kg body weight/day (iv). Another study, in rats, using a caprylic/capric triglyceride, confirmed that MCTs would not pose a concern with regard to potential developmental or reproductive effects at dietary levels up to 12,500 mg/kg body weight/day. There was no evidence that dietary administration of MCTs adversely affected the reproductive performance of pigs or resulted in maternal toxicity, foetal toxicity or teratogenic effects at doses up to 9375 mg/kg body weight/day in the diet. In rabbits following iv administration, the maternal and foetal NOAELs were between 1.0 and 4.28 g/kg body weight/day, with toxicity being associated with nutritional deficit in the dams. A 2-yr study in rats, conducted with a closely related compound (tricaprylin, a triglyceride with C_8 fatty acids), provided no evidence of a carcinogenic effect when the material was administered by oral gavage at levels up to 10 ml/kg (9.54 g/kg) per day. The toxicity NOAEL, based on data from this study, was 2.5 ml/kg/day (2.38 g/kg body weight/day). Although tricaprylin was found to be positive in one of five strains of *Salmonella typhimurium* in the presence of metabolic activation in an Ames microbial mutagenicity assay, the results of the carcinogenicity test with tricaprylin and mutagenicity tests with caprylic acid indicate that MCTs do not have the potential to be carcinogenic or mutagenic. The safety of human dietary consumption of MCTs, up to levels of 1 g/kg, has been confirmed in several clinical trials. MCTs have been used as 'Foods For Special Dietary Use' in a number of parenteral and enteral nutrient replacement products for many years (Gottschlich, 1992). MCT-containing products used for total parenteral nutrition contain approximately 20% MCTs, and depending on patient size and needs, are given in quantities of 1000 to 3000 ml/day (Ross, 1997). Thus, under maximum exposure conditions, a patient would receive 200–600 ml MCTs per day for up to several months. This would translate to 3.0 to 9.0 g/kg body weight/day (assume 70 kg body weight). Proposed uses in food would include MCTs at over a range of 4 to 67% of the food (for example granola bars 4%, muffins 8.3%, cheese 12–23%, mayonnaise 35% or margarine 67%), based on product preparation needs (Pao, 1982).

While there is an increase in the alveolar acetone levels in diabetic patients fed MCTs, there is no evidence to suggest that consumption of moderate levels of MCTs would contribute to ketosis in these patients. Studies in rats support the evidence for the absence of the risk for ketosis. In patients with cirrhosis or other liver disease there is the potential for higher circulating levels of free fatty acids due to reduced hepatic metabolism. However, there is no evidence that the consumption of moderate levels of MCTs would contribute to CNS effects such as hepatic encephalopathy in these patients. In the cases of the diabetic or the cirrhotic patient, the consumption of MCTs could not account for such an elevation of ketone bodies or of free fatty acids as would be required to trigger adverse effects.

Studies of MCTs carried out recently (e.g. Chanez, 1991; Webb 1993;) compared to those conducted years earlier (e.g. Klimmer, 1971; Kracht, 1963b) are consistent with regard to the observations that MCTs can be administered by various routes at relatively high dose levels, especially in the diet or by oral gavage, without significant adverse effect. NOAEL values from dietary studies appear to be consistently of the order of 3000–5000 mg/kg body weight/day and have been reported as high as 15,000 mg/kg body weight/day. Similarly, humans receiving MCTs parenterally have tolerated doses of 3.0–9.0 g/kg body weight/day for periods of several months without adverse effects. A standard 2500 cal/day diet, in which 30% of the dietary calories is fat (USDA, 1995) would include about 83.3 g fat per day. If 15% of the dietary calories, or 50% fat, were constituted of MCTs, the daily dietary intake of MCTs would be 41.7 g/day. For a 60-kg individual that would be about 0.7 g/kg body weight/day MCT. Compared to the lowest daily dose for TPN, about 200 ml or 3.2 g/kg body weight/day, the dietary intake would be 4.6-fold less than the intake used for TPN.

Conclusion

MCTs exhibit very low levels of toxicity in a variety of laboratory animals and in humans when administered orally, parenterally or by the dermal route. There is no evidence that MCTs are sensitizers and they show little evidence that they are ocular or dermal irritants. The data strongly suggest that MCTs would pose little or no risk from toxicity when consumed as a supplement in a balanced diet at levels up to 15% of the dietary calories or about 50% of the dietary fat.

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